BRIEF COMMUNICATION

Hereditary Retinoblastoma, Lipoma, and Second Primary Cancers

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Malignant connective tissue tumors, particularly soft-tissue sarcomas and osteosarcomas, are recognized complications of hereditary retinoblastoma (*1,2*). An apparent high frequency of lipomas, which are benign tumors of adipose tissue, among survivors of retinoblastoma was noted by a patient with hereditary retinoblastoma attending a recent meeting of the New England Retinoblastoma Family Support Group. Because we knew of no published reports of an association between germline mutations in the retinoblastoma (RB1) gene and lipomas, we examined data from a cohort of 898 retinoblastoma survivors, diagnosed at several New York hospitals during the period from 1914 through 1984. The study protocol was approved by the Institutional Review Boards of the National Cancer Institute and Westat, Inc. Written informed consent was obtained from all adult patients; written assent was obtained from juvenile patients, and written informed consent from their parents or guardians. Patients completed questionnaires in 1987-1988 and 1993-1994 about diagnoses and treatments of benign and malignant tumors. Frequencies of lipoma were compared between hereditary and sporadic retinoblastoma survivors.

The mean age (±standard error) of 556 patients with hereditary retinoblastoma when they completed their last questionnaire was 25.8 (±0.4) years (range, 4-64 years; median, 25.5 years), whereas the corresponding mean age of 342 patients with sporadic retinoblastoma was 27.5 (±0.6) years (range, 5-74 years; median, 27 years). Statistical analyses were based on comparisons of proportions, unadjusted for age differences. Odds ratios were estimated by conditional maximum likelihood methods, and exact 95% confidence intervals (CIs) and two-sided *P* values based on Fisher's exact test were calculated (*3*). Because of the younger average age of the patients with hereditary retinoblastoma, these unadjusted analyses may underestimate the risk associated with germline RB1 mutations.

Twenty (3.6%) of 556 patients with hereditary retinoblastoma and two (0.6%) of 342 with sporadic retinoblastoma reported diagnoses of lipomas (odds ratio [OR] = 6.3; 95% CI = 1.5-56.2; $P = .003$). The excess of lipomas among patients with hereditary retinoblastoma persisted after the analysis was restricted to the 13 patients with hereditary and the one with sporadic retinoblastoma whose lipomas were confirmed by use of clinical or pathology records (OR = 8.2; 95% CI = 1.2-347.9; $P = .023$). The incidence of lipomas in the general population is uncertain, because these lesions are infrequently excised or noted in medical records. On the basis of a population-based age distribution published in a Swedish study of lipomas (*4*), we estimated that 5.1 and 3.9 lipomas would have been expected in our hereditary and sporadic retinoblastoma cohorts, respectively, which corroborates the excess of lipomas among patients with hereditary retinoblastoma.

Sixty-eight (12.2%) of the patients with hereditary retinoblastoma and five (1.5%) of the patients with sporadic retinoblastoma had confirmed second cancers other than nonmelanoma skin cancer (OR = 9.4; 95% CI = 3.8-30.1; $P<10^{-6}$). Nineteen (86%) of the 22 patients with lipomas were men, which contrasts sharply with the almost equal sex distribution of patients with second cancers in the current cohort of retinoblastoma survivors (i.e., 37 men and 36 women; $P = .003$ for the test of the equality of this sex ratio and that of retinoblastoma patients with lipoma) and of patients with lipomas in the general population (*5*).

Six (30%) of 20 patients with hereditary retinoblastoma who had lipomas also developed second malignant neoplasms (Table 1) compared with 62 (12%) of 536 patients with hereditary retinoblastoma who did not report having had lipomas ($P = .025$), suggesting that certain RB1 mutations may increase the risk of both second cancers and lipomas. Three patients who had lipomas developed sarcomas (one patient developed a malignant fibrous histiocytoma, one developed a leiomyosarcoma, and one developed a fibrosarcoma). The sarcomas originated at sites distant from the lipoma in two of the patients, whereas the third patient had lipomas at multiple sites, including the scrotum where the leiomyosarcoma arose.

Our data suggest that lipomas, like sarcomas, may result from germline mutations in the RB1 gene (*6*). The clinical association between adult-onset lipomas and hereditary retinoblastoma might have escaped attention previously because physicians, even specialists, rarely see more than a few retinoblastoma survivors. Also, isolated findings of lipoma might not be entered in medical charts to be abstracted later through record reviews. The excess of lipomas in patients with hereditary retinoblastoma is not explained by ascertainment bias because of second cancer development, since the excess persists after patients who developed second cancers are excluded (OR = 4.9 [95% CI = 1.1-44.8] for reported diagnoses and OR = 5.6 [95% CI = 0.7-247.7] for confirmed diagnoses). Furthermore, the lipoma preceded the second cancer in three of the six case patients with second cancers, and only one case patient had both tumors excised concurrently (Table 1). The possibility that patients with hereditary cancer may be more vigilant or more likely to request excision of palpable masses should be explored in studies that involve an unselected series of retinoblas-

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See "Notes" following "References."

Table 1. Diagnostic data on lipomas and second cancers in 22 retinoblastoma survivors reporting diagnoses of lipomas

Retinoblastoma			Lipoma		Second cancer	
Type	Sex	Age at diagnosis, y	Site(s)	Age at diagnosis, y	Type and site	Age at diagnosis, y
Inherited	Male	1	Neck; back	40*		
	Female	2	Back; antecubital fossa	47*		
	Male	<1	Posterior neck	37*	Malignant fibrous histiocytoma, arm	41*
	Male	<1	Upper arm	37		
	Male	<1	Shoulder	27	Neuroblastoma, unknown site	36*
	Male	1	Posterior neck	22*	Carcinomas, tongue; melanoma, skin	20*
	Male	1	Spermatic cord; back	33*	Leiomyosarcoma, scrotum	33*
	Female	<1	Posterior neck	37		
	Male	1	Upper arm	28		
	Male	2	Posterior neck	30*		
	Male	2	Back	27*		
	Male	<1	Posterior neck	30*		
	Male	<1	Back	22*	Oxyphilic adenocarcinoma, parotid	34*
	Male	<1	Neck	28*		
	Male	<1	Back	28*	Fibrosarcoma, nasal cavity	26*
	Male	2	Chest wall	29*		
	Female	<1	Breast	22		
	Male	5	Leg	23		
	Male	2	Neck	25*		
	Male	1	Hip	----†		
Sporadic	Male	12	Back	31*		
	Male	2	Foot	31		

*Diagnosis confirmed.
†Age at lipoma diagnosis not specified.

toma survivors and include physical examinations.

Since somatic mutations in the RB1 tumor suppressor gene are common in sarcomas, it is noteworthy that cytogenetic studies of lipomas in general have revealed nonrandom changes in the chromosomal locus 13q14 that spans the RB1 gene (*7-9*). The link between hereditary retinoblastoma and lipoma would be strengthened by evidence of loss of the second (normal) RB1 allele in lipomas associated with retinoblastoma. Analyses of these lipomas for small deletions and point mutations in RB1 would also be informative, but technical difficulties may result from admixed normal cells and the large size (180 kilobases) of the gene (*10*).

Individuals with hereditary retinoblastoma are prone to development of dysplastic nevi with progression to cutaneous melanoma (*2,11*). Similarly, lipomas in patients with hereditary retinoblastoma may represent a clinical marker of susceptibility to sarcomas and other cancers, even though malignant changes in lipomas appear to occur very rarely, and only isolated cases have been reported (*4*). In view of the predominance of lipomas among men with germline RB1 mutations, further studies might examine the modifying influence of sex hormones or products of gene(s) on the sex chromosomes (*12*). Because retinoblastoma survivors are predisposed to melanocytic lesions and lipomas, their medical surveillance should include a careful examination of the entire body surface.

The findings of this study, prompted by a visually impaired but astute observer, illustrate the role of epidemiologic observations in generating new etiologic hypotheses in an era of powerful molecular technologies.

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Notes

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BOOK REVIEW

Diseases of the Breast
Jay R. Harris, Marc E. Lippman, Monica Morrow, Samuel Hellman, eds. Philadelphia: Lippincott-Raven, 1996. 1047 pp., illus. $169. ISBN 0-397-51470-0

Today, we are inundated by information about breast cancer in the scientific and lay press. Assimilation and interpretation of the emerging body of knowledge about this rapidly moving field is a problem for all scientific and medical professionals. *Diseases of the Breast* is the latest entry into this field. Edited by a multidisciplinary team of authorities in breast cancer, this textbook is a collection of 27 chapters from more than 100 authors and covers virtually all aspects of benign and malignant breast diseases. Included are chapters that deal with normal breast development and anatomy, clinical evaluation of the breast, techniques for breast biopsy, and management of common benign breast disorders. The remainder of the book focuses on a myriad of topics about breast cancer. Major areas include breast cancer biology and pathology, risk assessment and prevention, screening, staging, local management of in situ and invasive breast cancers, systemic treatment for early and advanced disease, and follow-up of breast cancer survivors. Smaller contributions cover a variety of special therapeutic problems in breast cancer, such as management of metastatic disease at specific sites, pregnancy and breast cancer, and male breast cancer. Sections on patient rehabilitation and support and organization of a comprehensive breast center reflect the relatively recent emphasis on breast cancer survivorship and health care delivery issues, respectively. About one third of the authors come from institutions associated with Harvard Medical School or Georgetown's Lombardi Cancer Center, reflecting the primary affiliations of two of the four editors.

The major strength of the book is its comprehensive scope. Over the last month I have referred to it for a range of questions from the most common (an overview of options for management of local recurrences after mastectomy) to the most esoteric (how to treat juvenile papillomatosis of the breast in an adolescent). Logical chapter organization and a good index made it easy to locate what I needed. Many chapters offer extensive reference lists to facilitate additional reading in a particular area. A particular strength of the book is its strong emphasis on breast cancer biology and its current and future implications for breast cancer prevention and management. A useful feature at the end of some (but unfortunately not all) of the clinically oriented chapters is a management summary that highlights key points about the treatment of the particular problem.

Diseases of the Breast is not immune to the problems that plague virtually all textbooks. Not surprisingly with 100+ authors, writing styles vary considerably, making some chapters much more readable than others. Overlap of material is unavoidable, although in some cases it is extensive, as in two sections that cover similar ground about the application of molecular techniques to the study of breast cancer. In other cases, topics seem unnecessarily fragmented. For example, the information in a small chapter on the breast conservation trials from the Milan National Cancer Institute would be better incorporated into the much larger section on local management of invasive breast cancer. Finally, the necessary delay between writing and publication means that information about several timely topics is already out-of-date. This is reflected particularly in the chapter on breast cancer genetics (which lacks the most recent information about BRCA1 and BRCA2) and the chapter on high-dose chemotherapy, another rapidly moving field.

The comprehensive nature of the book means that it will be an obligatory part of every institutional medical library. Its primary audience is the practicing physician, although some basic scientists may find it to be a useful source to obtain clinical information relevant to their work. Medical practitioners, like gynecologists who are involved in the field of women's health, will find it a welcome reference for all types of breast problems. However, the major beneficiaries will be the medical, surgical, and radiation oncologist, since breast cancer management is such a large part of all oncology practices. The editors state that "*Diseases of the Breast* is intended as a single-source compilation of the new knowledge on breast disease presented in a form accessible to practicing clinicians." Together with their coauthors, Drs. Harris, Lippman, Morrow, and Hellman have achieved this goal.

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Note

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